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Division of Dockets Management (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Docket No. 78N-0301; External Analgesic Drug Products for Over-The-Counter Human Use; Reopening of the Administrative Record and Amendment of Tentative Final Monograph (68 Fed. Reg. 42324)

Dear Sir or Madam:

The Mentholatum Co., Inc. ("Mentholatum" or "the Company") is grateful for the opportunity to provide comment on and data responsive to FDA's decision to reopen the administrative record for the above rulemaking proceeding. Patch, plaster, and poultice dosage forms of counterirritant active ingredient products were not specifically mentioned in the above referenced tentative final monograph ("TFM" or "the monograph") issued by FDA in 1983. Ever since, the significance of this omission has been the subject of frequent discussion not only between the Company and FDA but between the industry and the agency as well. This discussion has resulted in an agency effort to identify and a corresponding Company effort to collect the types of data needed to establish that there is no basis to exclude this specific dosage form from the applicability of a final monograph. As a result, the Company responds in this comment to the reopening of the administrative record in a currency with which FDA is familiar and has traditionally welcomed: reasoned analysis and objective data. The response substantiates the view that Mentholatum's patch/pad products are comparable to creams, lotions, and ointments and appropriately fall within the scope of the TFM.[1]

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[1] Mentholatum has been working closely with the Consumer Healthcare Products Association ("CHPA") in that organization's efforts to coordinate not only an industry-wide response to the reopening of the administrative record but also the development of labeling standardization and meaningful qualification procedures for new dosage forms. The Company endorses these efforts. The Company has opted to augment CHPA's comments with comments of its own because of the comprehensive product data and information the Company has assembled that are specific to Mentholatum® Arthritis Patch and Mentholatum® Pain Patch.

1. Background of the Proceeding

On February 8, 1983 (48 Fed. Reg. 5852), FDA published a tentative final monograph on OTC external analgesic drug products. The TFM stated that product labeling must identify the product "as an 'external analgesic,' 'topical analgesic,' or 'pain relieving (*insert dosage form, e.g., cream, lotion, or ointment).*'" *Id.* at 5858. FDA subsequently interpreted this language as encompassing only cream, lotion, or ointment-like dosage forms. As a result of this interpretation, FDA received a petition to clarify that the TFM applies to poultice or plaster dosage forms for the "counterirritant" active ingredients (*e.g.*, menthol, methyl salicylate) identified in the monograph. As part of its evaluation of the petition, FDA reviewed the report of the Advisory Review Panel on OTC Topical Analgesic, Anti-Rheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (published at 44 Fed. Reg. 69767, December 4, 1979). The agency found that there was little panel discussion and review of poultice or plaster dosage forms. FDA concluded that in order for a poultice and plaster dosage form to be generally recognized as safe and effective for an external analgesic drug product it would be necessary to obtain information documenting, specifically:

- the safe and effective concentration of the drug ingredients, especially under the occlusion of a plaster;
- data on percutaneous absorption under occlusion;
- the length of contact time that is safe to leave the poultice or plaster on the skin and how often the plaster or poultice needs to be changed for effective use;
- the frequency of application that is considered safe and effective;
- whether or not directions and a warning are necessary for use; and
- the age groups for whom poultices and plasters would be recommended for safe use.

This position prompted a number of industry submissions on external analgesic counterirritant active ingredients in dosage forms comparable to poultices and plasters -- including patch and pad dosage forms. Among the products noted in the submissions are Mentholatum patch/pad products. In the July 17, 2003 notice reopening the record of the TFM, FDA classified all such products as outside the scope of the TFM and as falling

within Category III. As discussed below, both legal and empirical bases compel the reconsideration of the agency's conclusions.

2. The Mentholatum Pain and Arthritis Patch Products

Mentholatum distributes two types of external analgesic OTC patch/pad products. Pain Patch contains a single active ingredient, menthol and is marketed in two strengths (4.26% and 5.0%). Arthritis Patch contains a single active ingredient, methyl salicylate (10.0%). The Company also distributes several private label menthol patch products containing 5.0% menthol.

Pain Patch (and its private label analogs) and Arthritis Patch fully conform with the ingredient dosage requirements of the TFM: the TFM provides that menthol is a safe and effective counterirritant when used in the range of 1.25% to 16% and that methyl salicylate is a safe and effective counterirritant when used in a range of 10% to 60%. 48 Fed. Reg. at 5852, 5868.

The pad used in Pain Patch and Arthritis Patch is soft and flexible and consists of a medicated hydrated ointment layer (commonly referred to as "gel layer") on non-woven, breathable cloth backing.[2] The gel layer is covered with a protective polyethylene terephthalate film. The polyethylene terephthalate film is removed prior to application of the pad to the skin and the gel layer is placed in direct contact with the skin. When applied, the gel layer conforms to the contour of the applicable body surface. The pad dosage system is, thus, similar to traditional poultices, lotions, ointments, and creams except that it provides the consumer with a convenient, non messy means of application. Each pad provides a predetermined quantity of active ingredient, thereby allowing consumers to consistently control drug dosing in a manner far better than can be achieved via creams, lotions, or ointments. Pain Patch and Arthritis Patch have been marketed for 10 and 2 years, respectively. Annual sales in 2002 for Pain Patch were nearly two million units and for Arthritis Patch were over 300,000.

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[2] Some confusion occasionally accompanies the use of the term "gel" in this context. The term is derived from the definition of "ointment" in the U.S. Pharmacopeia. The definition groups ointment vehicles into four general classifications. One of the classifications is "water soluble bases" which includes "greaseless ointment bases" that "contain no water-insoluble substances such as petroleum, anhydrous lanolin, or waxes." The USP observes that these ointments are "more correctly called Gels." USP 26, NF 21, 51 (2003).

3. Safety Concerns Are Not Presented By the Counterirritant Percutaneous Patch/Pad Dosage Form

a. Background

In crafting the OTC monograph rubric, FDA intentionally opted to focus on the safety and effectiveness of active ingredients and to avoid product specific evaluation. Over time, this focus has proven consistent with sound science, prevailing statutory authority as interpreted by the courts, and the public health. In this proceeding, the agency has departed from this practice by its exclusive focus on the propriety of including the patch/pad dosage form within the scope of the TFM. This is the case even though both Pain Patch and Arthritis Patch contain safe and effective concentrations of their respective active ingredients consistent with the TFM.

As noted above, the record of this proceeding indicates that this departure from customary FDA practice is primarily based on the agency's concern about systemic absorption of the active ingredients. The agency has also raised concerns regarding the potential of the patch/pad dosage form to cause dermal irritation and sensitization. Related concerns involve the frequency and duration of application, the adequacy of directions for use, and the need for and adequacy of warnings for use in general or by specific age groups.

All of the latter "related" concerns can be resolved by appropriate labeling provided the former concerns regarding the issues of absorption and dermal effects are resolved. To that end, data collected by The Mentholatum Company clearly show that Mentholatum's patch/pad products are non-occlusive. Similarly, data collected by the Company reveal that its patch/pad products are similar to other topical external analgesic products (like creams, lotions, and ointments) with regard to the potential for dermal irritation and sensitization. Mentholatum expressly commits to modify the labeling of its patch/pad products to address FDA's remaining concerns.

b. Occlusivity/Pharmacokinetic Testing

Agency concern has concentrated on the potential for the Company's patch/pad dosage form to increase absorption and, thus, potential toxicity of the active ingredient. Mentholatum's primary focus has been on methyl salicylate because serum salicylate levels have not been established to correlate well with methyl salicylate toxicity and further because methyl salicylate does not act like other commonly available salicylates when absorbed systemically (it has a much lower LD50, for example). These concerns were not resolved to the agency's satisfaction by the results of *in vitro* occlusivity testing the Company performed. As a result, after receiving comments from the agency, the Company decided upon and pursued a course of clinical study comparing the pharmacokinetics of topically applied methyl salicylate via the Company's patch/pad dosage form and via a 10% methyl salicylate cream and a 60% methyl salicylate cream.

The clinical study conducted was a comparative, open label, randomized three arm crossover investigation. The Company reviewed the administrative record for agency advice and comment regarding occlusivity testing and attempted to incorporate these as guidance in crafting the protocol for the study. The study population was 15 Caucasian men. The study duration was 12 hours and included 13 blood draws, one pre-application and thereafter one every 30 minutes for the first 4 hours and then one upon expiry of 5, 6, 9, and 12 hours. The clinical component of the study was conducted at International Research Services, Inc., Port Chester, NY. The analytical testing component of the study was undertaken by the National Medical Services, Inc., Willow Grove, PA. The protocol of the study and a report of the results are included under Tab A.

The study was thorough and comprehensive. The methodology for analyzing methyl salicylate in human plasma was validated and reliable. Pharmacokinetic variables, such as Cmax, Tmax, and AUC, were evaluated. Statistical analyses of the data were performed. The study results demonstrate that a 10% methyl salicylate patch/pad performs similarly to 10% methyl salicylate cream. Moreover, the study data reveal a lower Cmax for the patch/pad dosage form thereby indicating that the patch/pad may actually be a safer dosage form than the 10% cream. Without question, the data confirm that the patch/pad system provides a pharmacokinetic profile similar to those monograph dosage forms FDA has not called into question in this proceeding.

The data underscore the validity of the fundamental assumption as to ingredient rather than product status that has always accompanied the OTC monograph. These data in hand, FDA is fully justified in reading the TFM and its references to dosage forms like creams, lotions, and ointments as *examples* of specific dosage forms and *not* as a reflection of the intent to create exclusive categories of drugs delimited by dosage form.

The pharmacokinetic study also confirms the Company's position that the patch/pad dosage form is non-occlusive. To provide further evidence of non-occlusivity, the Company conducted new *in vitro* studies to investigate whether the patch/pad dosage form is similar or less occlusive than an ointment. In two studies, out-gassing in a closed capture cell was measured from the patch and a control ointment. One study measured out-gassing rates of Arthritis Patch and of a petrolatum-based ointment containing 10% methyl salicylate. The second study measured out-gassing rates of Pain Patch and of a petrolatum-based ointment containing 5% menthol. An occlusive covering is impermeable to water vapor or other volatiles across the structure. The study results demonstrate that vapors out-gas through the pad's backing at a greater rate than from an ointment form. The study reports for these investigations are provided under Tabs B and C. The upshot is straightforward: separate data sets clearly support the conclusion that the patch/pad dosage form is no more occlusive than ointments and creams. In sum, a reliable, empirical basis exists for interpreting the TFM as including the patch/pad dosage form and analgesic/counterirritant active ingredient methyl salicylate.

Although the Company has not ruled out the possibility of conducting a pharmacokinetic study of the topical delivery of menthol (Pain Patch) comparable to that conducted on methyl salicylate (Arthritis Patch), the results of such a study are not essential to resolution of the issues presented by the reopening of the administrative record. Unlike methyl salicylate, there are no specific science-based concerns regarding menthol absorption. The Company believes that the results of the pharmacokinetic study on the methyl salicylate patch/pad dosage form and the array of *in vitro* studies on both the methyl salicylate and menthol patch/pad dosage forms, coupled with the absence of specific concerns about the toxicity of menthol, provide a reasonable basis to recognize the safety of the menthol patch/pad dosage form and its inclusion in the TFM.

c. <u>Dermal Irritation and Sensitization Studies</u>

The record reveals a longstanding effort on the part of Mentholatum to document, through appropriately collected data, that the patch/pad dosage form does not meaningfully differ from other analgesic drug dosage forms (like creams, lotions, and ointments) in the potential to cause dermal irritation or sensitization. To confirm that the finished product does not possess the potential to cause dermal irritation or sensitization, the Company has conducted a Modified Irritation-Sensitization Screening Under Exaggerated Use Conditions on Pain Patch and Human Repeat Insult Patch Tests ("RIPT") on both the Pain Patch and the Arthritis Patch.

In the screening study under exaggerated use conditions protocol, the patch was applied three times per day for 14 days on the same site, followed by a rest period and a challenge at an alternate site. Dermatological observation and scoring were required and entered, respectively, three times per day for the 14 days. The study report is attached at Tab D. As can be seen, especially in the raw data included, the erythema resulting from this exaggerated use was characteristic of counterirritant formulations. The report concludes the product has a low order of potential for inducing acute irritation with repeated use and little or no potential as a sensitizing agent.

With respect to the subsequent RIPT tests on the products, the Company followed a standard, modified Draize protocol with repeat patching every three days over 21 days on the same site, followed by a rest period and then a challenge phase. This same protocol was also followed by the Company to evaluate external analgesic cream forms for potential for dermal irritation and sensitization. Study reports for the patch/pad products and a cream product are attached Tabs E, F, and G. Subjects included in the studies ranged from 16 to 75 years of age, with approximately 25% of subjects over age 55. The study results show that each external analgesic product is similar with no difference between dosage forms. Under the conditions of the studies, the products do not indicate a clinically significant potential for dermal irritation or allergic contact sensitization. A review of these results also reveals no correlation between age and observed erythema.

d. Complaint/Adverse Experience Reports

Mentholatum has systems in place to ensure the capture and review of complaints and appropriate categorization of adverse drug experience. Over the marketing history of these products, the Company has not received *any* reports of "serious" events as defined by MedWatch. The Company has, however, received consumer complaints involving burning, stinging, and causing redness or rash. The consumer complaints received reveal reactions typical of the mechanism of action of counterirritant drugs. *See* Tab H. As the External Analgesic Advisory Panel has observed, counterirritants achieve their beneficial effect by stimulating cutaneous sensory receptors and by producing a transient, reversible inflammation or irritation of the skin. 44 Fed. Reg. at 69779. In fact, counterirritants relieve pain indirectly by stimulating sensations of cold, warmth, and sometimes itching.[3] The Panel noted that it is expected that some individuals will overreact to the irritant properties of counterirritants and that, for those individuals, a label warning like "Discontinue use if condition worsens or if symptoms persist for more than 7 days and consult a physician" is the reasonable and effective way of addressing these side effects. *Id.* at 69780.[4] Other occasional complaints relate to the removal of the patch/pad.

The incidence of complaints is low -- based on annual complaint and sales data the worst case scenario is less than one complaint for every 30,000 packages of product sold. Moreover, the complaints primarily concern the minor discomfort caused by the counterirritant itself and are not related to the dosage form.

Without question, the marketing history, including the complaint and adverse experience history, reveals a long track record for the safety of the patch/pad dosage form. It is reported that FDA's External Analgesic Advisory Panel recognized years ago the role of the marketplace in the OTC review process. A focus on safety and efficacy, as opposed to individual dosage forms, was viewed as appropriate because

> The marketplace will assist in determining which vehicle is preferable and this choice ought not to be "regulated." It was argued that the Panel should be concerned with whether or not the consumer could do himself any harm if he chooses one type

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[3] Handbook of Nonprescription Drugs, 12 ed., American Pharmaceutical Association, 2000.

[4] To avoid "improper use" the Panel also suggested the caution "Do not bandage." The TFM amended this to "Do not bandage tightly," indicating that some form of bandaging is appropriate. 48 Fed. Reg. at 5869. Unlike a traditional "bandage," the patch/pad delivery system has a breathable cloth backing that, unlike tight bandages, permits out-gassing.

of vehicle over another. The consensus of the dermatologists present was that it does not matter.[5]

The Company's marketplace data confirm that consumers have on a consistent and increasing basis opted to use -- and continue to use -- topical analgesic products in patch/pad dosage form.

e. Relevant Scientific Literature

CHPA has commissioned an extensive search of the scientific literature for information relevant to the safe and effective use of patch/pad dosage forms for the delivery of counterirritant drugs. Only a small number of relevant abstracts, reports, and articles have been found. Of these, only a few citations address safety, occlusivity, or pharmacokinetics and none are as specific or probative as Mentholatum's research on the issue. Importantly, no significant reports of population specific sensitivities have been found. In two placebo-controlled studies (Keitel et al. 2001 and Kim et al. 2002), efficacy responses to capsaicin plasters were highly significant vs. placebo. Both active and placebo plasters were well tolerated and the researchers described the benefits of the dosage form. Keitel et al. reported only mild adverse reactions, which they associated with the active ingredient. In another study (Horn and Enge, 1982), the researchers were unsuccessful in their attempt to use a capsaicin plaster to induce erythema in order to test an unrelated hypothesis. Their conclusion was the plaster provided a weak inflammatory effect. In a study designed to demonstrate age –specific responses to capsaicin, (Munce and Kenney, 2003), the researchers soaked the pad of a bandage with varying concentrations of capsaicin in alcohol solution and applied these 'patches' to the skin for a short period of time. A vehicle soaked pad was included as a placebo control. Differences in skin blood flow, the measured response, were seen between young, middle-aged, and older individuals. The age-based difference was also seen in both the placebo patch and in baseline response. While the intensity of the response varied with capsaicin concentration, again this is seen to be related to the active ingredient, capsaicin, and not the 'patch' dosage form. In sum, researchers have used the patch/pad dosage forms as a convenient vehicle for applying counterirritants, have found such forms to be well-tolerated by study subjects, and have not observed any untoward side-effects inherent to these dosage forms.

The literature is consistent with the Company's data and product experience and provides no independent basis for excluding patch/pad dosage forms from the TFM and any resulting final monograph. Nothing of substance in the publicly available literature provides a basis for questioning the "general recognition" of safety and effectiveness of the

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[5] Unofficial Summary Report of the Second Meeting of the Topical Analgesic, Anti-Rheumatic, Otic, Burn, Sunburn Treatment and Prevention FDA OTC Review Panel, prepared by Joseph L. Kanig, Ph.D., Industry Liaison, (May 8-9, 1973).

Pain Patch and Arthritis Patch products. And, in fact, the publicly available literature supports such recognition.

f. Summary

The agency's concerns with regard to absorption and irritation and sensitization of patch/pad products are expressly addressed and favorably resolved by the data and information collected, assembled, and submitted to the record of this proceeding by Mentholatum. Those data consistently reveal that the patch/pad dosage form performs similarly to other analgesic drug dosage forms. In fact, the data indicate the patch/pad dosage form may result in a less occlusive drug delivery system than ointments or creams. Moreover, because the patch/pad delivery system contains a measured dose of drug, there is less likelihood for over or under medication than that presented by creams, lotions, and ointments. Tellingly, marketplace and complaint data and information reveal widespread product acceptance. No age-specific or special population-based concerns are suggested by study data or product experience. Simply put, no science-based reason exists for either interpreting the TFM or applying the OTC process in a manner that deprives an increasing number of consumers of uninterrupted access to a safe active drug ingredient in a dosage form they desire, prefer, and seek out.

4. Product Labeling and Conformity with the TFM is an Effective Tool for Addressing Remaining Agency Concerns

Current product labeling for Mentholatum's Pain Patch and Arthritis Patch are consistent with and conform to the requirements of the tentative final monograph. Tab I. Mentholatum has always believed in the wisdom of and need for employing dosage levels deemed effective by FDA for creams, lotions, and ointments. The Company's pharmacokinetic data confirm the comparability of the patch/pad dosage form to creams, lotions, and ointments and, thus, support the Company's decision to employ dosage levels compliant with the TFM.

In an effort to ensure proper, effective use of its patch/pad products, Mentholatum has included in its product labeling additional warnings and instructions comparable to those listed in the TFM as well as those appearing on counterirritant creams, lotions, and ointments. For example, while the TFM requires the warning "Avoid contact with the eyes," the Pain Patch provides "Do not get into eyes or on mucous membranes." Similarly, the tentative final monograph requires the statement "Do not bandage tightly," while the Pain Patch and Arthritis Patch labels expressly provide "Do not bandage tightly or cover with any type of wrap except clothing;" "Do not use with a heating pad or apply external heat;" and "Do not use in combination with other external analgesic products."

Moreover, the labeling of both patches provides that a pad should be changed 1-2 times daily. The label for each product also emphasizes that the products are for the

"temporary relief" of "minor" aches and pains of muscles and joints. And, the labeling of each product provides that use should be stopped if pain persists for more than 7 days.

Product experience reports do not reveal any significant consumer problems with regard to understanding or use arising from product labeling. And, of course, the labeled directions for use and warnings are consistent with the safety data and information collected by the Company and submitted to the agency. Under these circumstances, there is no basis upon which to reasonably question the adequacy of product labeling to address agency concerns. Nevertheless, the Company recognizes the valuable role product labeling plays in the OTC arena and commits to crafting product labeling that addresses concerns FDA concludes need to be addressed.

5. The Counterirritant Percutaneous Patch/Pad Dosage Form is Appropriate for OTC Status

a. The Scope of the Tentative Final Monograph is Inclusive

The record of this proceeding is replete with legal arguments proffered not only by Mentholatum but also by other manufacturers of patch/pad analgesic dosage forms that the tentative final monograph should necessarily be interpreted to be dosage form-blind and, thus, include the patch/pad dosage form. *See*, for example, The Mentholatum Company's Citizen Petition to Reopen the Tentative Final Monograph for External Analgesic Drug Products for OTC Use, August 3, 1995; Letter to Robert Heller (HFD-312) from Donald E. Segal re: Monograph Compliance of Mentholatum's Pain Patch, October 5, 1994; see also Responses 1, 7, and 18 from the agency's July 17, 2003 notice (68 Fed. Reg. at 42327). At the heart of this argument, advanced herein as well, is the fact that the OTC review was established to determine which OTC drug active ingredients are safe and effective. The agency's focus in the OTC review has traditionally been on the drug ingredient not the dosage form. As a result, over the years, a number of different dosage forms have been accommodated under the OTC rubric. Mentholatum continues to believe that the best legal interpretation of the tentative final monograph is that FDA is obligated to similarly accommodate the patch/pad dosage form in the tentative final monograph. Nevertheless, the Company does not proffer this position as its primary basis for seeking agency acknowledgment that the Mentholatum pain and arthritis patch products appropriately fall within the scope of the tentative final monograph. Instead, the Company has attempted to respond empirically to the agency's concerns regarding these products and address them by the collection and submission of reliable, objective data.

For thoroughness, the Company does, however, incorporate by reference into this comment the legal arguments it has presented in the past in support of inclusion. And, in the following sections the Company also identifies other legal and policy-based reasons supporting such inclusion. The Company offers these arguments and reasons not only to support its position but, importantly, to provide additional comfort to the agency that the

requested inclusion is not only sound scientifically but also completely in accord with prevailing legal precedent and sound public health policy.

b. <u>Precedent and Current Agency Practice Support Inclusion of the Patch/Pad Dosage Form</u>

The agency recently published a final monograph establishing conditions under which OTC skin protectant drug products are generally recognized as safe and effective. 89 Fed. Reg. 33362 (June 4, 2003). The final monograph includes skin protectant drug products for minor cuts, scrapes, burns, etc. This particular monograph process began in 1978 with an advance notice of proposed rulemaking based on the recommendations of the Advisory Review Panel on OTC Topical Analgesic, Anti-Rheumatic, Otic, Burn and Sunburn Prevention and Treatment Drug Products -- the panel whose review prompted the February 8, 1983 tentative final rule on external analgesic drug products. In addressing comments concerning the statement of identity for skin protectant products, the agency focused on the need to add a description of the dosage form to the statement, e.g., "skin protectant (dosage form)". In support of including the dosage form in the statement of identity, the agency reasoned as follows:

> The United States Pharmacopeia (USP) lists a number of dosage forms that might be used for OTC topical drug products .... From a marketplace survey ..., the agency finds that the most widely used dosage forms for OTC skin protectant drug products are lotions, creams, ointments and gels. The examples of dosage forms listed in the statement of identity in ... this final monograph *are not all inclusive and depend on products' historical marketing as skin protectants.*

68 Fed. Reg. at 33363 (emphasis supplied).

The response reveals the longstanding agency practice to resist limiting the applicability of a monograph. The response also confirms that the inclusiveness of a monograph is not limited to the most widely-used dosage forms and the historical marketing of a dosage form is an important determinant of the scope of a monograph. External analgesic/counterirritant patch/pad dosage forms have been marketed for decades. FDA has even acknowledged the probability that such products were marketed well before the external analgesic drug monograph proceedings began. *See* April 7, 1995 letter from Bradford Williams, Division of Labeling Compliance, Center for Drug Evaluation and Research, FDA to Yasuhiro Yamada, the Mentholatum Company.

A similar agency display of the practice of listing in a TFM dosage forms *as examples*, not as delimiters, is seen in the preamble to the final monograph of topical acne

drugs for OTC use, 56 Fed. Reg. 41008 (August 16, 1991). There, after noting that salicylic acid may be included in a formulation of 0.5 to 2% in a suitable dosage form ("cream," "gel," or "lotion"), the agency observed "other dosage forms would also be acceptable ... based on their previous marketing history for this type of product." *Id.* at 41020. In spite of their limited history of use, the agency included "pads" as an example of such other dosage forms.

The external analgesic TFM, as noted earlier in this comment, contains language comparable to that employed in the above examples regarding the *types* of dosage forms applicable, "cream, lotion, or ointment" (48 Fed. Reg. at 5858). In light of current usage and past precedent, if the agency meant to be exclusive, it would have said so. In fact, once FDA channels its discretion in a certain direction, the agency must follow that course consistently or articulate sound reasons for departure. *Rhodia, Inc. v. FDA*, 608 F.2d 1376, 1379 (D.C. Cir. 1979). No reasons for such a departure are present here: as the data supplied by Mentholatum establish, no scientific basis exists for excluding Mentholatum's patch/pad products from the TFM or treating the products less favorably than products in cream, lotion, or ointment dosage form.

c. Mentholatum's Patch/Pad Dosage Form Products Are Entirely Distinct from Transdermal Patch Dosage Forms

If any confusion remains regarding the distinction between Mentholatum's patch/pads and transdermal delivery systems, it may be addressed and dispensed with quickly. The distinction between the Mentholatum patch/pad dosage form and transdermal patch dosage forms is addressed by the USP. As the USP explains, transdermal drug delivery systems are "designed" to deliver drugs "through the skin to the systemic circulation." USP 26 at 2406. Drugs like Mentholatum's are "for local rather than systemic effect" and are commonly applied to the skin "embedded in glue [adhesive] on a cloth or plastic backing." *Id.* at 2406. Although the USP refers to these products as "plasters or tapes," the categorization clearly encompasses the patch/pad form. Thus, the structure and function of the patch/pad form are fundamentally different from transdermal drug delivery systems. And, in fact, as Mentholatum's pharmacokinetic data confirm, the products differ dramatically in systemic effect.

d. Mentholatum's Patch/Pad Dosage Form Is Comparable to Creams, Lotions, and Ointments As a Drug Delivery System

The conclusion to which this entire comment leads is captured in the above heading. Simply put, reliable, objectively collected data regarding the effect of the patch/pad dosage form support the conclusion that Mentholatum products' patch/pad dosage form is comparable to creams, lotions, and ointments as a drug delivery system. Marketing history and product experience with regard to the Company's patch/pad dosage form products support this conclusion. Moreover, the non-substantive differences that do exist

between the patch/pad dosage form and those like creams, lotions, and ointments can be communicated to the consumer in product labeling in terms that not only are likely to be read but also will be understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use.[6]

6. As A Matter of Law, the TFM Should Be Interpreted As Including Counterirritant Percutaneous Patch/Pads Like Mentholatum's Pain and Arthritis Patches As An Acceptable Dosage Form

Concluding that the Mentholatum patch/pad dosage form falls within the scope of the TFM is justified by scientific evidence and is consistent with prevailing legal authority and agency precedent. In the context of OTC use, "safety" means a low incidence of adverse reactions or significant side effects associated with a drug. 21 CFR 330.10(a)(4). This "safety" is, of course, circumscribed within the scope of intended use and premised on the ability of a manufacturer to provide adequate directions for use and warnings against unsafe use. Embedded in the notion of the safety of an OTC drug is also the notion that there is a low potential for harm that may possibly result from abuse arising from the widespread availability of an OTC drug. The data and information regarding the Mentholatum patch/pad products all support the conclusion that these requirements are met for the Company's products.

In the context of an OTC drug, "effectiveness" means the reasonable expectation that in a significant proportion of the target population, the intended effect of the drug will be achieved when the drug is used under its intended and labeled conditions of use. *Id.* The dosages of drug in the Mentholatum products fall within the ranges identified in the TFM as "effective." The Company's pharmacokinetic data confirm the propriety of these dose ranges for Mentholatum's patch/pad products and the comparability of the patch/pad dosage form and creams, lotions and ointments. The record of this proceeding clearly supports the "effectiveness" of the Mentholatum patch/pad dosage form products under the established OTC standard.

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[6] The comparability of patch/pad dosage form and ointments, creams, and lotions is established in Europe. The European Pharmacopoeia has established a monograph for "Semi-solid Preparations for Cutaneous Application. The monograph equates ointments, creams, pastes, poultices, and medicated plasters. The patch/pad dosage form falls within the monograph's definition of "medicated plasters."

The OTC process has played a vital role in the U.S. healthcare system by providing consumers easy access to those drugs that can be used safely for conditions that consumers can self treat without the help of the healthcare practitioner. The Mentholatum patch/pad products empirically belong in that class of drugs. To interpret them as appropriate for such status is consistent with sound science, the empirical record of this proceeding, and agency practice and precedent. Under these circumstances, Mentholatum believes that it would be unlawful for FDA to interpret the TFM and any resulting final monograph as not including the patch/pad dosage form. The unlawfulness of such an interpretation would arise from what could only be an arbitrary and capricious disregard for the facts and precedent. And, of course, the immediate impact on Mentholatum from any such interpretation would be unjustified, irreparable harm.

Conclusion

In light of the foregoing and in light of the comments offered on behalf of the industry by CHPA, the Mentholatum Company respectfully requests FDA to interpret the tentative final monograph in this proceeding and any resulting final monograph as including the patch/pad dosage form.

Sincerely,

Joyce L. Miller

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Director, Regulatory Affairs

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Submitted by Fax

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Re: October 14, 2003 Comments to Docket No. 78N-0301; External Analgesic Drug Products for Over-the-Counter Human Use; Reopening of the Administrative Record and Amendment of Tentative Final Monograph

Dear Sir or Madam:

We wish to assure FDA that The Mentholatum Company does not claim any privilege for anything in the material submitted on October 14, 2003. This information is considered part of the public docket.

Sincerely,

Joyce L. Miller

Joyce L. Miller
Director, Regulatory Affairs

The Mentholatum Co., Inc.

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FAX TRANSMITTAL

DATE: October 28, 2003

TO: Latroy Tinch
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FROM: Joyce L. Miller
Director, Regulatory Affairs
Ext. 1572

TOTAL PAGES: 2

In response to your telephone contact, please see attached letter regarding The Mentholatum Company's comments to Docket No. 78N-0301 on October 14, 2003.